Remarks

Claims 1, 3-5, 8, 11-13, 125, 127 and 130 are currently amended. Support for amendment to claims 1 and 130 can be found in claims 1, 2, 14 and 130 as previously pending (particularly in view of claim 3). Claims 3-5, 8 and 11-13 are amended to depend from a pending rather than a now cancelled claim. Claims 125 and 127 are amended to be consistent with now amended claim 1.

Claims 2, 10 and 14 are cancelled. Applicants reserve the right to pursue the subject matter of claim 10 in a continuing application.

Claims 131 and 132 are added. Support for these claims can be found in claims 1 and 130 as previously pending.

Claims 1, 3-9, 11-13, 15-28 and 125-132 are pending.

No new matter has been added.

Claims Fees

Applicants previously paid for 38 total claims (i.e., 18 in excess of the 20 allowed with the basic filing fee) and 11 independent claims (i.e., 8 in excess of the 3 allowed with the basic filing fee). There are currently 33 total claims and 4 independent claims pending. Accordingly, no additional claims fee is considered due.

Rejection under 35 U.S.C. §112, first paragraph

Claims 1-10, 12, 14-22, 24-28 and 125-130 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. According to the Examiner, the specification enables

> "a method for inducing a mucosal immune response comprising administering to a mucosal surface of a subject an effective amount for inducing a mucosal immune response of an oligonucleotide having a length of at least 8 nucleotide residues and including the elected species of 5'X1X2CGX3X4 (i.e., GTCGTT), wherein both C and G are unmethylated; and administering to the subject an antigen not encoded in a nucleic acid vector to the subject, thereby inducing the mucosal immune response."

The Examiner disputes that the specification enables methods involving CpG oligonucleotides of less than 8 nucleotides. The claimed invention relates only to

oligonucleotides of at least 8 nucleotide residues, and more specifically to oligonucleotides 8-100 nucleotides in length.

The Examiner also disputes that the specification enables methods involving CpG oligonucleotides in which only the C is unmethylated. The Examiner bases this on his interpretation of the prior art meaning of "unmethylated CpG motif". Applicants maintain that the Examiner has misunderstood the prior art meaning of the term. The significance of unmethylated CpG motifs and their utility in stimulating immunity revolves around the initial observation that bacterial DNA could be immunostimulatory. Bacterial DNA can be distinguished from mammalian DNA based on methylation status of cytosine residues within CpG dinucleotide motifs; generally mammalian DNA is methylated at such sites while bacterial DNA is not. The methylation status of the guanosine residue is largely irrelevant as it is usually unmethylated in both bacterial and mammalian DNA and thus could not be the cause of the differing properties of these nucleic acids. Accordingly, the term "unmethylated CpG" is understood in the art to correspond to an unmethylated cytosine conjugated to a guanosine. "Unmethylated", therefore, refers to the cytosine. This is further supported in the instant specification which clearly states on page 19, lines 1-2 that "at least the C of the 5' CG 3' must be unmethylated". The specification including the Examples provided therein demonstrate, inter alia, the immunostimulatory properties of CpG oligonucleotides comprising an unmethylated cytosine conjugated to a guanosine. Accordingly, such a claim limitation is enabled by the specification and the working examples.

The Examiner further disputes that the specification enables methods involving passive exposure to an antigen. Applicants strenuously disagree with the Examiner and wish to highlight the inconsistency in the Examiner's position with respect to enablement of passive antigen exposure. The Examiner maintains that passive exposure is not enabled in the §112 rejection. Concurrently, the Examiner asserts USP 6,218,371 in the §103 rejection. Any reference used in a rejection must itself be enabling; thus the Examiner acknowledges that USP 6,218,371 is enabling. Moreover, if the cited reference is a U.S. patent, then it further enables all that it claims. USP 6,218,371 claims a method for stimulating an antigen specific immune response by administering a particular cytokine and a CpG nucleic acid to a *subject that is exposed to an antigen.* The subject need not be administered the antigen, but rather only passively exposed to the antigen in order to effect the antigen specific immune response. Accordingly, methods of

inducing antigen-specific immune responses in subjects that are passively exposed to an antigen are known and enabled, as acknowledged by the USPTO and the Examiner.

Notwithstanding the above and for the sake of expediting prosecution of this application, Applicants have amended claims 1 and 130 to read on active exposure of a subject to an antigen (i.e., administration of an antigen to a subject). By this amendment, however, Applicants are not conceding to the Examiner's arguments. Concurrently, Applicants introduce new claims 131 and 132 which recite passive antigen exposure of the subject. Applicants draw the Examiner's attention to previously filed responses, the recently filed Declaration of Heather L. Davis, and USP 6,218,371 as evidence that antigen-specific immunity is achieved upon passive exposure of a subject to an antigen following CpG oligonucleotide administration, and that this immunity is not subject-dependent.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph, enablement.

Rejection under 35 U.S.C. §102(e)

Carson US 20030109469

Claims 1-10, 12, 14-22, 24-28 and 125-130 are rejected under 35 U.S.C. §102(e) as being anticipated by Carson (US 20030109469) as evidenced by Moldoveanu et al. Vaccine vol. 16, page 1216, 1998, McCluskie et al (IDS C2) and McCluskie et al. Vaccine vol. 18, pp. 413-422, 2001.

The Examiner bases his rejection at least in part on the misunderstanding that the oligonucleotide of the claimed invention can be "a nucleic acid vector comprising a CpG motif in the non-coding sequence". The oligonucleotide of the claimed invention is not a plasmid expression vector. See for example, page 15, lines 31 continuing to page 16, line 1 where it is stated that "the oligonucleotide, referred to herein as the oligonucleotide or the CpG oligonucleotide, is not a plasmid" and page 19, lines 5-6 where it is stated that "a CpG oligonucleotide and a plasmid expression vector are mutually exclusive." In addition, claims 1 and 130 have been amended to recite an oligonucleotide length of 8-100 nucleotides. Carson teaches recombinant gene expression vectors and their use in enhancing immune responses of a host to an antigen. Carson clearly defines "naked gene expression vectors" as "plasmids or cosmids which include at least one non-coding, immunostimulatory polynucleotide region, (that)

preferably also encode a peptide of interest (e.g., antigens and cytokines) and are not associated with a delivery vehicle." The remaining references are moot as to their evidentiary weight because the Carson reference does not anticipate the claimed invention.

Furthermore, Applicants wish to correct a statement made by the Examiner in reference to the administration routes of oligonucleotide and antigen in the claimed invention. The claimed invention recites that the oligonucleotide is administered to a mucosal surface of the subject. However, the antigen may be administered in a variety of ways and is not limited to mucosal administration. Notwithstanding this, Carson still does not anticipate the claimed invention.

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejection under 35 USC §102(e) in view of Carson.

Rejection under 35 U.S.C. §103(a)

Carson US 20030109469 taken with Krieg et al. 6,218,371

Claims 1-10, 12, 14-22, 24-28 and 125-130 are rejected under 35 U.S.C. §103(a) as being unpatentable over Carson (US 20030109469) taken with Krieg (6,218,371).

The Examiner is directed to the response under 35 USC § 102(e) with respect to Carson. Simply, Carson teaches the importance of expression vectors in stimulating an antigen-specific immune response, preferably to an antigen encoded by the expression vector. The claimed invention relates to the use of oligonucleotides, particularly those that are 8-100 nucleotides in length. These are clearly not plasmids.

The Examiner and Applicants continue to disagree about the status of the Krieg reference as a prior art reference. The status of the Krieg reference however is irrelevant in view of the teaching in Carson regarding the importance of expression vectors in inducing an immune response. The instant claims relate to oligonucleotides; these are defined in the specification to exclude plasmids and are now recited in the claims as being 8-100 nucleotides in length. Thus, at a minimum the combination of Carson and Krieg does not render obvious the claimed invention at least because Carson states the importance of expression vectors (and not oligonucleotides) as the immunostimulatory agent.

Notwithstanding the above and for the record, Applicants traverse the Examiner's position with respect to the previously submitted Declaration of Heather L. Davis. The

Examiner challenges the recently filed Declaration of Heather L. Davis on the basis that it does not provide any factual evidence that "the combined use of cytokine including B-7 as an adjuvant in combination with CpG containing oligos of at least 8 nucleotides was conceived of and reduced to practice prior to the effective filing date of Krieg." The Examiner also states that the Declaration does not provide substantial evidence "that the use of GTCGTT as an adjuvant was conceived of and reduced to practice prior to the effective filing date of Krieg." The Declaration demonstrates that the instant inventors knew prior to the effective filing date of Krieg (i.e., April 3, 1998) and at least as early as November 1997 that mucosal administration of a CpG oligonucleotide could induce a mucosal immune response to an antigen upon antigen exposure. Accordingly, Krieg is removed as a prior art reference.

In addition, Applicants wish to point out that the Examiner's reliance on Krieg 6,218,371 indicates the Examiner's position that this reference is enabling. Applicants agree that the reference is enabling. In particular, Applicants point out that claim 1 provides a method for stimulating an immune response in a subject comprising administering to a subject "exposed to an antigen" ... an immunopotentiating cytokine ... and an immunostimulatory CpG oligonucleotide ... " and claim 7 provides for a subject that "is passively exposed to the antigen". Accordingly, the Examiner has taken and continues to take contradictory positions with respect to enablement of induction of antigen-specific immunity via passive exposure to antigen.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §103(a).

Briles et al. (USP 6,042,838) in view of Carson US 20030109469 taken with Krieg et al. (WO 96/02555)

Claims 1-10, 12, 14-22, 26-28 and 125-130 are rejected under 35 U.S.C. §103(a) as being unpatentable over Briles et al. (USP 6,042,838) in view of Carson (US 20030109469) taken with Krieg et al. (WO 96/02555).

The Briles and Krieg references have been discussed in the previous response and the Examiner is referred thereto. The Examiner previously made and then withdrew a §103(a) rejection in view of the Briles and Krieg references, thereby indicating that the combination of Briles and Krieg references does not render the claimed invention obvious. The addition of Carson does not provide the deficiency in the combined teaching of Briles and Krieg, at the very

least because Carson teaches the importance of expression vectors as adjuvants. Accordingly, the combination of Briles, Carson and Krieg does not render obvious the claimed invention either.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103(a).

Summary

Applicants believe that each of the pending claims is in condition for allowance. Should the Examiner disagree, **Applicants respectfully request a telephone interview with the Examiner prior to the issuance of a further action**.

Respectfully submitted,

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